



US005643464A

United States Patent [19]

Rhee et al.

[11] **Patent Number:** **5,643,464**[45] **Date of Patent:** **Jul. 1, 1997**[54] **PROCESS FOR PREPARING A STERILE,
DRY CROSSLINKING AGENT**

[75] **Inventors:** **Woonza M. Rhee**, Palo Alto; **Richard A. Berg**, Los Altos; **Joel S. Rosenblatt**, Palo Alto; **Jacqueline A. Schroeder**, Redwood City; **Larry J. Braga**, Fremont; **Thomas L. Smestad**, Palo Alto; **Abigail Freeman**, Fremont, all of Calif.

[73] **Assignee:** **Collagen Corporation**, Palo Alto, Calif.

[21] **Appl. No.:** **497,573**

[22] **Filed:** **Jun. 30, 1995**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 287,549, Aug. 8, 1994, which is a continuation-in-part of Ser. No. 236,769, May 2, 1994, Pat. No. 5,475,052, which is a continuation-in-part of Ser. No. 198,128, Feb. 17, 1994, Pat. No. 5,413,791, which is a division of Ser. No. 922,541, Jul. 30, 1992, Pat. No. 5,328,955, which is a continuation-in-part of Ser. No. 433,441, Nov. 14, 1989, Pat. No. 5,162,430, which is a continuation-in-part of Ser. No. 274,071, Nov. 21, 1988, abandoned.

[51] **Int. Cl.⁶** **B01J 19/08**; A01N 1/02; A61F 2/00

[52] **U.S. Cl.** **210/748**; 250/432 R; 250/492.1; 250/492.3; 378/64; 378/66; 422/22

[58] **Field of Search** 422/22; 210/748; 250/455.11, 432 R, 492.1, 492.3; 378/64,

66

[56] **References Cited****U.S. PATENT DOCUMENTS**

4,865,602	9/1989	Smestad et al.	623/16
5,162,430	11/1992	Rhee et al.	525/54.1
5,292,802	3/1994	Rhee et al.	525/54.1
5,306,500	4/1994	Rhee et al.	424/422
5,328,955	7/1994	Rhee et al.	525/54.1

Primary Examiner—Nathan M. Nutter

Attorney, Agent, or Firm—Kathi Rafayko

[57] **ABSTRACT**

The present invention discloses a novel method for preparing crosslinked biomaterial compositions for use in the augmentation of soft or hard tissue. In general, the method comprises mixing a biocompatible polymer, which is preferably collagen, with a sterile, dry crosslinking agent, which is preferably a synthetic hydrophilic polymer such as a functionally activated polyethylene glycol. Also provided are preferred processes for preparing sterile, dry crosslinking agents contained within syringes for use in the method of the invention. Methods for sterilization of the crosslinking agent include, but are not limited to, sterile filtration, aseptic processing, and e-beam or gamma irradiation. Methods for providing augmentation of soft or hard tissue using crosslinked biomaterial compositions prepared according to the method of the invention are also disclosed.

5 Claims, 1 Drawing Sheet